Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure

ExTraMATCH II Collaboration

DOI:
10.1016/j.jacc.2018.12.072

Title:
Impact of exercise-based rehabilitation in patients with heart failure (ExTraMATCH II) on exercise capacity and health-related quality of life: a ~~systematic review and~~ meta-analysis of individual participant data from randomised trials

Brief title: Exercise-based HF rehabilitation: HRQoL and exercise capacity

Authors names:

Professor Rod S Taylor [a], PhD
Dr Sarah Walker [a], PhD
Professor Neil A Smart [b], PhD
Professor Massimo F Piepoli [c], MD PhD
Dr Fiona C Warren [d], PhD
Dr Oriana Ciani [a,e], PhD
Professor David Whellan [f], MD MHS
Professor Christopher O'Connor [g], MD
Professor Steven J Keteyian [h], PhD
Professor Andrew Coats [i], DM
Associate Professor Constantinos H Davos [j], MD
Associate Professor Hasnain M Dalal [a, k], MD
Professor Kathleen Dracup [l], PhD
Professor Lorraine S Evangelista [m], PhD
Professor Kate Jolly [n], PhD
Professor Jonathan Myers [o], PhD
Associate Professor Birgitta B Nilsson [p], PT PhD
Professor Claudio Passino [q], MD
Professor Miles D Witham [r], PhD
Associate Professor Gloria Y Yeh [s], MD
on behalf of the ExTraMATCH II Collaboration.

Total word count:
6088

Author affiliations:

[a] Institute of Health Research, University of Exeter Medical School, UK
[b] University of New England, Armidale, Australia
[c] Cardiology Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy
[d] Exeter Collaboration for Academic Primary Care, Institute of Health Research, University of Exeter Medical School, UK
[e] Centre for Research on Health and Social Care Management, Bocconi University, Milan, Italy
[f] Department of Medicine, Sidney Kimmel Medical College, Philadelphia, Pennsylvania, USA
[g] Duke Clinical Research Institute, North Carolina, USA
[h] Department of Medicine, Henry Ford Hospital, Detroit, Michigan, USA
[i] IRCCS, San Raffaele, Pisana, Italy

[j] Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, Athens, Greece
[k] Research, Development & Innovation, Royal Cornwall Hospital, Truro, UK
[l] School of Nursing, University of California San Francisco, USA
[m] University of California Irvine, California, USA
[n] Institute of Applied Health Research, University of Birmingham, UK
[o] VA Palo Alto Health Care System / Stanford University, California, USA
[p] Division of Medicine, Oslo University Hospital and Faculty of Health Sciences, Oslo Metropolitan University, Norway
[q] Fondazione G. Monasterio and Scuola Superiore Sant'Anna, Pisa, Italy
[r] NIHR Newcastle Biomedical Research Centre, Institute of Neuroscience, Faculty of Medical Sciences,, Newcastle University, Newcastle, UK
[s] Beth Israel Deaconess Medical Center, Department of Medicine, Boston, Massachusetts, USA

Funding:

National Institute for Health Research Health Technology Assessment Programme (NIHR-HTA 15/80/30).

Disclosures:

RST and HMD are currently co-chief investigators and KJ a co-investigator on a National Institute for Health Research (NIHR) funded programme grant designing and evaluating the clinical and cost-effectiveness of a home-based cardiac rehabilitation intervention for heart failure patients (RP-PG-1210-12004). KJ is part funded by NIHR CLAHRC West Midlands. All other authors declare no conflicts.

Address for correspondence:

Professor Rod Taylor, Institute of Health Research, University of Exeter Medical School, College House, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU, England, United Kingdom.
r.taylor@exeter.ac.uk

Twitter
The ExTraMATCH II individual participant meta-analysis of 19 randomised clinical trials confirms the benefit of ExCR on HRQoL and exercise capacity in heart failure patients

@ExeterECG
@rod_ExeterECG
@Sarah1003Walker

Acknowledgments:

This study presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. We acknowledge the contribution of patient data from Dr Rebecca Gary, Dr Rainer Hambrecht, the late Dr

Romualdo Belardinelli, and the late Dr Pantaleo Giannuzzi. We thank Mr Tim Eames, Exeter Clinical Trials Unit, for his advice and support on data management for this study.

Abstract

Background: Previous systematic reviews have indicated that exercise-based cardiac rehabilitation (ExCR) for patients with heart failure (HF) has a beneficial effect on health-related quality of life (HRQoL) and exercise capacity. However, there is uncertainty regarding potential differential effects of ExCR across HF patient subgroups.

Objectives: To undertake an individual participant data (IPD) meta-analysis to; (i) assess the impact of ExCR on HRQoL and exercise capacity in patients with HF, and (ii) to investigate differential effects of ExCR according to a range of patient characteristics: age, sex, ethnicity, New York Heart Association (NYHA) functional class, ischaemic aetiology, ejection fraction, and exercise capacity.

Methods: A single dataset was produced, comprising randomised trials where ExCR (delivered for 3 weeks or more) was compared with a no exercise control group. Each trial provided IPD on HRQoL or exercise capacity (or both), with follow-up of 6 months or more. We used one- and two-stage meta-analysis models to investigate the effect of ExCR overall and the interactions between ExCR and participant characteristics.

Results: IPD was obtained from 13 trials for 3990 patients, predominantly (97%) with reduced ejection fraction HF. Compared with control, there was a statistically significant difference in favour of ExCR for HRQoL and exercise capacity. At 12-month follow-up, improvements were seen in 6-minute walk test (mean: 21.0 metres, 95% CI: 1.57 to 40.4, p=0.034) and Minnesota Living with HF score (mean improvement: 5.9, 95% CI 1.0 to 10.9, p=0.018). No consistent evidence was found of differential intervention effects across patient subgroups.

Conclusions: These results, based on an IPD meta-analysis of randomised trials confirm~~s~~ the benefit of ExCR on HRQoL and exercise capacity and supports the Class I recommendation of current international clinical guidelines that ExCR should be offered to all HF patients.

Keywords:
Rehabilitation, heart failure, quality of life, exercise capacity, QoL, MLHFQ

Condensed Abstract

The effect of exercise-based cardiac rehabilitation (ExCR) on HRQoL and exercise capacity for patients with heart failure was investigated using one- and two-stage meta-analysis on individual participant data from 13 randomised trials (3990 patients)

At 12-month follow-up, improvements were seen in 6-minute walk test and Minnesota Living with HF score. No consistent evidence was found of differential intervention effects across patient subgroups. These results confirm the benefit of ExCR on HRQoL and exercise capacity, supporting the Class I recommendation of current international clinical guidelines that ExCR should be offered to all HF patients.

Abbreviations

CI	Confidence interval
ExCR	Exercise-based cardiac rehabilitation
HF	Heart failure
HFpEF	HF with preserved ejection fraction (≥45% ejection fraction)
HFrEF	HF with reduced ejection fraction (<45% ejection fraction)
HRQoL	Health-related quality of life
IPD	Individual participant (or patient) data
KCCQ	Kansas City Cardiomyopathy Questionnaire
MLHFQ	Minnesota Living with Heart Failure Questionnaire
Peak VO_2	Peak oxygen uptake

Introduction

Heart failure (HF) is a major public health problem with substantial morbidity and mortality and is a burden to patients and health systems. (1) Whereas survival after HF diagnosis has improved, prognosis remains poor; 30 to 40% of patients die within a year of diagnosis. (2) Patients living with HF experience marked reductions in their exercise capacity which has detrimental effects on their health-related quality of life (HRQoL).

With increasing numbers of people living longer with symptomatic HF, the effectiveness and accessibility of health services for HF patients have never been more important. Exercise-based cardiac rehabilitation (ExCR) is widely recommended in clinical guidelines as integral to the comprehensive care of HF patients. (3-7) ExCR is a process by which patients, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health. (3) In addition to exercise training, it is now accepted that ExCR programmes should be comprehensive and include education and psychological care, as well as including advice on health and life-style behaviour change. (3, 4)

Systematic reviews and trial level data meta-analyses have shown ExCR offers important health benefits for HF patients compared with control. (8-10) Based on data from 26 randomised trials with median follow up of 12.4 months, Uddin et al reported a mean improvement in peak oxygen uptake (peak VO_2) of 2.79ml/kg/min (95% CI: 2.05 to 3.53) following ExCR. (9) The 2014 Cochrane review reported a clinically important improvement across 13 RCTs in disease-specific health-related quality of life (HRQoL) as assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) up to 12-month follow-up (mean score -5.8 points, 95% CI: -9.2 to -2.4) compared with control. (8) Using meta-regression analysis, these meta-analyses found no association between trial level patient characteristics (age, gender, ejection fraction) and ExCR on either exercise capacity or

HRQoL. However, such analyses are highly prone to study-level confounding (ecological fallacy) and should be interpreted with great caution. Uncertainty therefore remains as to whether there are differential effects of ExCR on exercise capacity and HRQoL across HF patient subgroups. (11) Individual participant data meta-analysis is increasingly be recognised as the gold standard approach for assessing intervention subgroup effects. (11, 12) Whilst a previous IPD meta-analysis (ExTraMATCH) reported the impact of ExCR on clinical events (death and hospitalisation) it did not consider the outcomes of exercise capacity or HRQoL. (13)

Using IPD meta-analysis, this ExTraMATCH II study aimed to assess the impact of ExCR on HRQoL and exercise capacity and to investigate differential effects of ExCR across subgroups of patients with HF.

Methods

This study was conducted and reported in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA IPD) statement and current guidance on the use of IPD. (14, 15) Our full study protocol has been published elsewhere and is registered on the Prospero database of systematic review protocols (CRD42014007170). (16, 17) The clinical events results has been published elsewhere. (18)

Search strategy and selection criteria

Trials were identified from the original ExTraMATCH IPD meta-analysis carried out in 2004 and updated with trials identified in the 2014 Cochrane systematic review of ExCR for HF. (8, 13) The Cochrane review searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, EMBASE, MEDLINE, CINAHL, PsycINFO, and the NHS Centre for Reviews and Dissemination (CRD). Conference proceedings were searched on Web of Science. Trial registers (Controlled-trials.com and Clinicaltrials.gov) and reference lists of all eligible trials and identified systematic reviews were also checked. No language limitations were imposed. Details of the search strategy used are reported elsewhere. (16, 17)

Trials were included if they met the following criteria: (i) randomised trials of adult patients (aged 18 years and older) with a diagnosis of HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) based on objective assessment of left ventricular ejection fraction and clinical findings; (ii) ExCR intervention that delivered an

aerobic exercise training component involving the lower limbs, lasting a minimum of 3 weeks, either alone or as part of a comprehensive cardiac rehabilitation programme (which may also include health education and/or a psychological intervention); (iii) a comparator arm which did not prescribe an exercise intervention; (iv) a minimum follow-up of 6 months and (v) and a sample size of more than 50 (to ensure that the logistical effort in obtaining, cleaning and organising the data was commensurate with the contribution of the data set to the analysis). (19, 20)

Data management

Principal investigators of studies were invited by email to participate in this IPD meta-analysis and share their anonymised trial data. Patients in the clinical trials providing data gave their consent on entry to the original clinical trial. All included datasets had ethical approval and consent from their sponsors; they were not required to seek additional ethical approval for the inclusion of their data in this analysis. The complete list of all requested variables and details on collaboration with principal investigators are reported in the study protocol. (8) Data from each trial were checked on range, extreme values, internal consistency, missing values, and consistency with published reports. Trial investigators were contacted about data discrepancies or missing information. Each anonymised dataset was saved in its original format and then converted and combined into one overall master dataset. All files were stored on a secure password protected computer server managed and in accordance with the data management standard operating procedures of Exeter Clinical Trials Unit, a UK Clinical Research Collaboration (UKCRC) registered clinical trials unit. Access to data at all stages of cleaning and analysis was restricted to the Exeter research team (OC, RST, SW and FCW).

Specification of outcomes, subgroups, and risk of bias assessment

Health-related quality of life (HRQoL) and exercise capacity data were obtained from trial investigators at the patient level. HRQoL was recorded as one of three validated measures: (i) Minnesota Living with Heart Failure Questionnaire (MLHFQ) (21); (ii) Kansas City Cardiomyopathy Questionnaire (KCCQ) (22) and (iii) Guyatt Chronic Heart Failure scale (23). The first analysis was performed using only MLHFQ data; the second analysis used a standardised score calculated from any of the three measures above. As MLHFQ reports higher HRQoL as a lower score, the scales of the KCCQ and Guyatt Heart Failure score (which report higher HRQoL as a higher score) were reversed before standardising so that the directionality would be the same as MLHFQ. Therefore, for both the MLHFQ score and standardised HRQoL score, an improvement in HRQoL is shown by a reduction in the overall score.

Exercise capacity was recorded as one of four validated exercise capacity measures: (i) peak VO_2 (ml/kg/min); (ii) distance (metres) walked in a 6-minute walk test (6MWT); (iii) distance (metres) walked in an incremental shuttle walk test (ISWT) and (iv) cycle ergometer watts. Two of these measures, peak VO_2 and 6MWT, analysed as separate outcomes. A third outcome, a standardised exercise capacity score for patients with any validated exercise capacity measure, was also analysed. The large HF-ACTION trial (24) provided data on both peak VO_2 and 6MWT and was included in all analyses, with the peak VO_2 measure taking precedence for the standardised exercise capacity score.

We also sought IPD on the following pre-defined subgroups: age, gender, ejection fraction (HFpEF (≥45% ejection fraction) vs. HFrEF (<45% ejection fraction)), New York Heart

Association (NYHA) functional class, HF aetiology (ischaemic vs. non-ischaemic), ethnicity (white vs. non-white), and baseline exercise capacity. Study quality and risk of bias were assessed using the TESTEX quality assessment tool. (25)

Statistical analysis

A detailed statistical analysis plan was prepared (available from authors). All analyses were carried out according to the principle of intention to treat (i.e. patients analysed as randomised) and included all patients providing the data required for each model. All one-stage and two-stage analyses used random effects models as the overall dataset is likely to include a high degree of clinical heterogeneity across the individual trials due to differences in population, exercise-based rehabilitation intervention and comparator intervention. (26) All results are reported as a between group mean difference (ExCR-control) with a 95% confidence interval (CI) and p-value.

The primary analyses comprised one-stage and two-stage IPD meta-analyses carried out at two follow-up times: 6 and 12 months. For all analyses, we used the observation at, or closest prior to, the analysis time. Using this criterion, more trials had available data at 12-month follow-up than at 6-month follow-up. Therefore, we have regarded the 12-month data analyses as being the primary analyses. The results at 12-month follow-up are reported ahead of the 6-month results in order to optimise the number of trials included.

One-stage IPD models used a hierarchical random effects regression model, adjusted for the baseline value of the outcome measure. We ran a series of models to estimate the overall treatment effect and to investigate potential interactions between ExCR and pre-defined

patient subgroups (age, gender, left ventricular ejection fraction (< 45% or ≥ 45%), heart failure aetiology (ischaemic vs non-ischaemic), NYHA class (I/II vs III/IV) and baseline exercise capacity (16, 17)). Each model investigated one interaction effect only. We used two-stage random effects models as a sensitivity analysis to estimate the effect of ExCR. The τ^2 and I^2 statistics were reported alongside the associated p-value for the results of the main analyses.

The secondary analyses used a random effects hierarchical model which took account of the repeated measurement of the outcome (HRQoL or exercise capacity) over the duration of each trial. These models utilised outcome data at all available time points. Adjustments for baseline values of the outcome measure were made; no other covariates were included in the model. This model included a time by treatment interaction term.

To test the robustness of the primary analyses, pre-specified sensitivity analyses were carried out. First, each primary analysis was repeated after exclusion of the largest trial, HF-ACTION. (24) Second, aggregate data from studies that did not provide IPD was added and the impact on meta-analysis conclusions assessed. We checked for potential small study bias by assessing funnel plot asymmetry and using the Egger test. (27) Additional plots of the results of the one-stage IPD meta-analysis models, stratified by patient characteristics, are presented in order to give the reader a visual representation of the differential effect of ExCR in each subgroup. All analyses were undertaken using Stata 14.2 StataCorp LP, College Station, Texas, USA.

Results

Selection and inclusion of studies

Of the 23 trials identified either in the ExTraMATCH IPD meta-analysis (13) or the 2014 Cochrane systematic review of ExCR for HF (8, 16), we were unable to include data from three trials (355 patients); for two trials data was no longer available (28, 29) and the investigators of the third trial could not be contacted. (30)

Of the 20 trials remaining, one trial (31) was excluded due to an overlap between patients included in another identified trial. (32) Thirteen studies provided anonymised individual participant data (IPD) for analysis of HRQoL and exercise capacity outcomes. (24, 32-43) Published trial-level data was available for an additional five trials for each of the HRQoL (28, 29, 44-46) and exercise capacity analyses. (28-30, 44, 45) In addition to comparing usual care to an intervention arm of usual care plus ExCR, Gary (35) also compared the effects of cognitive behaviour therapy to cognitive behaviour therapy plus ExCR. For the purpose of analysis from this point forward, this will be described as one trial providing two comparators and be analysed as separate trials from this point forward.

For the HRQoL analysis, 9 trials (including 10 comparator groups) provided data for 3000 patients (1496 ExCR, 1504 control) with a median follow-up of 33 weeks. (24, 34, 35, 38-43) For the exercise capacity analysis, 13 trials (14 comparator groups) provided 3332 patients (1662 ExCR, 1670 control) with a median follow-up of 26 weeks. (24, 32-43) Figure 1 summarises the study selection process.

Study, patient, and trial characteristics

Patient baseline characteristics were well balanced between ExCR and control patients (Table 1). The majority of patients were male (73%) with a mean age of 61 years. The mean baseline left-ventricular ejection fraction was 27%; fewer than 3% of patients had preserved ejection

fraction heart failure (defined as ejection fraction > 45%). Most patients were in NYHA functional class II (62%) or III (36%). Studies were published between 2000 and 2012 across Europe and North America. Sample size ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention; four also included resistance training. (34, 38, 40, 41) Four trials (five comparators) were conducted in an exclusively home-based setting (34, 35, 38, 43); all other trials delivered ExCR in a centre-based setting. The dose of exercise training varied across studies; average session duration ranged from 15 to 60 minutes (including warm-up and cool-down); minimum number of sessions per week was 2, with a maximum of 7; exercise intensity equivalent ranged from 40 to 70% peak $VO_{2;}$ and the duration of intervention ranged from 4 to 120 weeks. (Table 2)

Quality of included trials

The overall quality of included trials was judged to be moderate to good, with a median TESTEX (25) score of 11 (range 9 to 14) out of a maximum score of 15 (~~eTable~~Online Appendix Table 1). The criteria of allocation concealment and physical activity monitoring in the control groups were met in only two (24, 38) and three studies (24, 34, 42), respectively. The other TESTEX criteria were each met in at least 50% of trials.

Effect of intervention on outcomes

One-stage meta-analysis showed a significant improvement in HRQoL for those on the ExCR intervention compared with control, as assessed by the MLHFQ, at 12-month follow-up: (mean improvement: 5.9, 95% CI 1.0 to 10.9, p=0.018, τ^2 =77, I^2 =88%) (~~Online Table~~Online Appendix Table 2) and standardised HRQoL score (mean improvement 0.20 standard

deviation units, 5% CI 0.03 to 0.37, p=0.020, τ^2 =0.07, I^2 =85%) (~~Online Table~~Online Appendix Table 3). Similar results were seen at 6-month follow up. Two-stage meta-analysis results were comparable and are presented graphically for ~~6~~12-month follow-up (Figure 2) and ~~6~~12-month follow-up (Figure 3).

Compared with control, treatment effects from the one-stage meta-analysis at 12-month follow-up showed a statistically significant improvement with ExCR in exercise capacity as assessed by 6MWT (mean difference: 21.0 metres, 95% CI: 1.6 to 40.4, p=0.034, τ^2 = 491, I^2 =78%) (~~Online Table~~Online Appendix Table 5) and standardised exercise capacity score (mean difference: 0.27 standard deviation units, 95% CI 0.11 to 0.43, p=0.001, τ^2 =0.08, I^2 =91%) (~~Online Table~~Online Appendix Table 6). No significant difference in peak VO_2 at 12 months was observed: 1.01 (95% CI -0.42 to 2.44, p=0.168, τ^2 = 2.17, I^2 =94%) (~~Online Table~~Online Appendix Table 4).

In the repeated measures analyses for each HRQoL and exercise capacity outcome, a significant interaction between ExCR and time was observed (~~Online Figure~~Online Appendix Figure 1). In sensitivity analyses, the results of the analyses excluding HF-ACTION, were broadly consistent with the overall results (Online Appendix ~~e~~Tables 3, 4, 5 and 6). Similar results were found with the addition of the trial-level aggregate data to the two-stage model at 12-month follow-up.

There was no evidence of significant small study bias for the five outcomes studied (~~Online Figure~~Online Appendix Figure 2).

Differential effects across subgroups

Analyses revealed no consistent interaction between the effect of ExCR and the predefined subgroups gender, ejection fraction, NYHA class, HF aetiology, ethnicity, and baseline exercise capacity for either HRQoL or exercise capacity (~~eTable~~Online Appendix Tables 2, 3, 4, 5 and 6 and ~~Online Figure~~Online Appendix Figures 3-4).

A differential effect of ExCR across ages was observed in the standardised HRQoL score analysis at 6-month follow-up, with a differential reduction in HRQoL in the ExCR group compared with the control group (i.e. an increase in standardised HRQoL score) as age increased (0.006 standard deviation units, 95% CI 0.002 to 0.011, p=0.006) (~~Online Table~~Online Appendix Table 3). To put this into context, based on a standard deviation of 24 for MLHFQ score, this equates to a mean increase of 1.4 in MLHFQ score (ie: a reduction in HRQoL) for an increase of 10 years in patient age, in the ExCR group compared with the control group.

Interaction analyses for the one-stage model at 12 months showed differential effects of ExCR by gender, with women showing greater benefit from ExCR than men for each of peak VO_2 (0.57 ml/kg/min, 95% CI: 0.04 to 1.11, p=0.036) and 6MWT (14.9m, 95% CI: 1.2 to 28.7, p=0.034) (~~Online Table~~Online Appendix Table 4). Differential effects of ExCR were also seen between ethnic groups (~~Online Table~~Online Appendix Table 5); white patients showed a greater improvement with ExCR in 6MWT distance compared with non-white patients: 14.2m (95% CI: 0.40 to 28.0, p=0.044).

Discussion

We undertook an IPD meta-analysis to assess the impact of ExCR on exercise capacity and HRQoL in patients with HF. Analyses of data from 13 trials in 3990 randomised patients, predominantly (97%) with reduced ejection fraction HF, showed some evidence that ExCR improves both exercise capacity and HRQoL compared with no exercise control 12-month follow-up, with weaker evidence for a treatment effect at 6-month follow-up. The magnitude of the treatment effect of ExCR on MLHFQ score observed at 12-month follow-up was not only statistically significant but also clinically important, (47) with a mean between group difference of >5 points, favouring the ExCR group. Also, there was an increase of ≥ 16 metres in the 6MWT in the ExCR group, which may also be clinically significant. (48) Interaction analyses showed that younger patients responded better to ExCR in terms of improved HRQoL; women and white patients had a better exercise capacity response. However, the interactions between ExCR and age, gender and ethnicity were not consistent across health outcomes, different analyses, and time points. The findings should therefore be considered hypothesis generating.

We believe this to be the first IPD meta-analysis to assess the impact of ExCR on HRQoL and exercise capacity outcomes for patients with HF. The observed beneficial effects of ExCR on these outcomes are broadly consistent with previous trial-level (aggregate data) meta-analyses. (8-10, 49) The improvement (reduction) in MLHFQ score was similar to that reported by the 2014 Cochrane meta-analysis (5.8, 95% CI: 2.4 to 9.2). (8) The improvements in exercise capacity outcomes observed in our analyses were lower than those seen in trial-level meta-analyses (6MWT: 41.1 metres, 95% CI: 16.7 to 53.6 (31); peak VO2: 2.79 ml/kg/min, 95% CI: 2.05 to 3.53). (9) We found no consistent evidence of HF patient subgroup effects, in accord with trial level meta-regression analyses. (8, 9) Within trial subgroup analyses from the HF-ACTION trial found no differential effect of ExCR on

HRQoL across patient characteristics. (50) A post-hoc analysis of the same trial cohort reported a significant interaction between ExCR and ethnic group with regard to 6MWT distance at 3-month follow-up (adjusted p=0.02), with mean improvement compared with control of 26m (95% CI: 18 to 34) in white HF patients versus 11m (95% CI: 0 to 21) in black HF patients, in the same direction as the current study. (51)

Study limitations

IPD meta-analysis has a number of strengths relative to traditional trial-level meta-analysis, including: reduction in ecological biases; the ability to check and transform data to common scores or measures; consistent methods of analysis across trials, and improved power to detect overall and subgroup effects. In this study, we used a one-stage meta-analysis approach to compare the outcomes between ExCR and control groups across all included trials. This approach adjusts the between-group comparisons of outcomes at follow-up for the baseline outcome score; this is important here as many of the included studies were small and therefore subject to chance differences in baseline score. Given these considerable advantages, meta-analyses that are based on IPD have been called the 'gold standard' of systematic review. (12)

An increasingly recognised challenge of IPD meta-analysis is that of obtaining IPD from study investigators. (15, 52) A recent systematic review across a total of 122 IPD meta-analyses found the average meta-analysis located only 61% (95% CI: 46% to 74%) of eligible data sets. (53) In this study we were able to retrieve patient data for all 13 trials with exercise capacity data; HRQoL data was available in 9 out of 13 (69%) trials for 89% (2970/3332) of participants. Although our level of data retrieval compares favourably with this recent

systematic review, we recognise that incomplete data capture is a limitation of our study, which may have introduced bias to our HRQoL analyses. Furthermore, we observed high levels of statistical heterogeneity for the outcomes of MLHFQ and 6MWT, likely to be due to the variation in population and intervention characteristics across the individual trials. Reassuringly, the inclusion of published results of trials for which no IPD was available did not change main effects. Due to limited published data on patient characteristics, we were unable to perform any sensitivity analyses using subgroup data.

Further important limitations of this analysis were the small number of patients with HFpEF that contributed to this analysis and the lack of data on patient level ExCR 'dose'. We did not have patient level data on 'ExCR dose' received, so we were unable to explore the effect of patient adherence to the rehabilitation program, or duration, frequency or intensity of ExCR undertaken by an individual patient.Trials that include larger proportions of patients with HFpEF would enable us to address the question of whether ExCR has a differential effect in such patients compared to those with HFrEF. Improved reporting of patient level data on adherence to ExCR will enable the investigation of any `dose–response' effect of ExCR. With regard to generalisability and application to clinical practice, the average age of participants in this study was 61 years, whereas the average age of HF patients in practice is approximately 10 years older. (54)

Conclusions

Provision of ExCR to patients with HFrEF produces clinically important benefits in HRQoL and exercise capacity. Although we did observe some differences in the treatment effect of ExCR with age, gender, and ethnicity, these subgroup effects were not consistent across

outcomes, time points and analyses; hence, our findings do not endorse limiting ExCR interventions to subgroups of HF patients. However, due to the low numbers of women and non-white patients participating in ExCR, ExTraMATCH II would support the increasing representation of these groups. These results, based on an IPD meta-analysis of randomised trials, support the Class I recommendation of current international clinical guidelines that ExCR should be offered to all HF patients and the need to improve current poor uptake of ExCR in this population. Future data collection in this field requires a consensus on the definition, collection, and reporting of core outcomes, including a defined minimum standardised set of outcomes that should be measured and reported in all clinical trials in specific areas of health or health care. (55) Additionally we call for capture of data on patient level adherence to exercise training during the ExCR intervention period. Future trials should be extended to include more women, older patients and more patients with HFpEF, as well as patients with comorbid conditions. More generally, the research community should continue to implement policies that encourage primary study authors to make their datasets available, either by depositing their datasets in publicly available repositories or sharing with IPD meta-analysis collaborations when directly requested.

Contributors

RST and SW take joint responsibility for lead authorship. RST, NS, MP, OC, FCW designed the study and obtained the study funding. SW analysed the data. All authors contributed to writing and editing of the manuscript, with the lead taken by RST and SW. CO'C, KD, LSE, RG, RH, KJ, JM, BBN, CP, MDW, GYY and ADZ contributed individual participant data for this study. All authors commented on the manuscript and agreed the final version.

Acknowledgments: This study presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. We acknowledge the contribution of patient data from Dr Rebecca Gary, Dr Rainer Hambrecht, the late Dr Romualdo Belardinelli, and the late Dr Pantaleo Giannuzzi. We thank Mr Tim Eames, Exeter Clinical Trials Unit, for his advice and support on data management for this study.

Declaration of interests: RST and HMD are currently co-chief investigators and KJ a co-investigator on a National Institute for Health Research (NIHR) funded programme grant designing and evaluating the clinical and cost-effectiveness of a home-based cardiac rehabilitation intervention for heart failure patients (RP-PG-1210-12004). KJ is part funded by NIHR CLAHRC West Midlands. All other authors declare no conflicts.

Funding: National Institute for Health Research Health Technology Assessment Programme (NIHR-HTA 15/80/30).

Role of the funding source: The funders peer review process informed the study protocol. The sponsor of the study had no role in data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit.

Perspectives:

Competency in Medical Knowledge: Exercise-based cardiac rehabilitation improves HRQoL and exercise capacity in patients with heart failure, irrespective of patient characteristics.

Translational Outlook 1: Future trials need to evaluate the effect of exercise-based cardiac rehabilitation in patient groups more representative of the current population of patients with heart failure.

Translational Outlook 2: A consensus on the definition, collection and reporting of core outcomes in all clinical trials should be reached.

Translational Outlook 3: Individual participant data on adherence to exercise-based cardiac rehabilitation should be collected in randomised controlled trials.

References

1. Braunwald E. The war against heart failure: the Lancet lecture. Lancet. 2015;385(9970):812-24.

2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137-46.

3. BACPR. Standards and core components for cardiovascular disease prevention and rehabilitation 2017. Available from: www.bacpr.com/resources/6A7_BACR_Standards_and_Core_Components_2017.pdf.

4. Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. The BMJ. 2015;351.

5. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013;128(16):1810-52.

6. Kondamudi N, Haykowsky M, Forman DE, Berry JD, Pandey A. Exercise Training for Prevention and Treatment of Heart Failure. Prog Cardiovasc Dis. 2017;60(1):115-20.

7. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting Physical Activity and Exercise: JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(14):1622-39.

8. Taylor RS, Sagar VA, Davies EJ,et al. Exercise-based rehabilitation for heart failure. Cochrane Database of Systematic Reviews. 2014(4).

9. Uddin J, Zwisler AD, Lewinter C, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis. Eur J Prev Cardiol. 2016;23(7):683-93.

10. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. Am J Med. 2004;116(10):693-706.

11. Thompson S, Higgins J. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.

12. Chalmers I. The Cochrane Collaboration: Preparing, Maintaining, and Disseminating Systematic Reviews of the Effects of Health Care. Annals of the New York Academy of Sciences. 1993;703(1):156-65.

13. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). The BMJ. 2004;328(7433):189.

14. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for a systematic review and meta-analysis of individual participant data: The PRISMA-IPD statement. JAMA. 2015;313(16):1657-65.

15. Tierney J, Vale C, Riley R, et al. Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. PLoS Med. 2015;12(7):e1001855.

16. Taylor R, Piepoli M, Smart N, et al. Exercise training for chronic heart failure (ExTraMATCH II): protocol for an individual participant data meta-analysis PROSPERO [Internet]. 2014. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42014007170.

17. Taylor RS, Piepoli MF, Smart N, et al. Exercise training for chronic heart failure (ExTraMATCH II): Protocol for an individual participant data meta-analysis. Int J Cardiol. 2014;174(3):683-7.

18. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. Eur J Heart Fail. 2018.

19. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. The BMJ. 2010;340.

20. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. The BMJ. 2012;344.

21. Bilbao A, Escobar A, García-Perez L, Navarro G, Quirós R. The Minnesota living with heart failure questionnaire: comparison of different factor structures. Health Qual Life Outcomes. 2016;14:23.

22. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245-55.

23. Guyatt GH, Nogradi S, Halcrow S, Singer J, Sullivan MJJ, Fallen EL. Development and testing of a new measure of health status for clinical trials in heart failure. J Gen Intern Med. 1989;4(2):101-7.

24. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure: HF-ACTION Randomized Controlled Trial. JAMA. 2009;301(14):1439-50.

25. Smart NA WM, Ismail H, Giallauria F, Vigorito C, Cornelissen V, Dieberg G. Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. Int J Evid Based Healthce. 2015;13(1):9-18.

26. Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. The BMJ. 1997;315(7109):629-34.

28. Davidson PM, Cockburn J, Newton PJ, et al. Can a heart failure-specific cardiac rehabilitation program decrease hospitalizations and improve outcomes in high-risk patients? Eur J Prev Cardiol. 2010;17(4):393-402.

29. Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. Eur J Heart Fail. 2005;7(3):411-7.

30. Klecha A, Kawecka-Jaszcz K, Bacior B, et al. Physical training in patients with chronic heart failure of ischemic origin: effect on exercise capacity and left ventricular remodeling. Eur J Prev Cardiol. 2007;14(1):85-91.

31. Myers J, Goebbels U, Dzeikan G, et al. Exercise training and myocardial remodeling in patients with reduced ventricular function: One-year follow-up with magnetic resonance imaging. Am Heart J. 2000;139(2, Part 1):252-61.

32. Mueller L, Myers J, Kottman W, , et al. Exercise capacity, physical activity patterns and outcomes six years after cardiac rehabilitation in patients with heart failure. Clin Rehabil. 2007;21(10):923-31.

33. Belardinelli R, Georgiou D, Cianci G, Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. J Am Coll Cardiol. 2012;60(16):1521-8.

34. Dracup K, Evangelista LS, Hamilton MA, et al. Effects of a home-based exercise program on clinical outcomes in heart failure. Am Heart J. 2007;154(5):877-83.

35. Gary RA, Dunbar SB, Higgins MK, Musselman DL, Smith AL. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. J Psychosom Res. 2010;69(2):119-31.

36. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. Circulation. 2003;108(5):554-9.

37. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. JAMA. 2000;283(23):3095-101.

38. Jolly K, Taylor RS, Lip GY, et al. A randomized trial of the addition of home-based exercise to specialist heart failure nurse care: the Birmingham Rehabilitation Uptake Maximisation study for patients with Congestive Heart Failure (BRUM-CHF) study. Eur J Heart Fail. 2009;11(2):205-13.

39. Nilsson BB, Westheim A, Risberg MA. Long-term effects of a group-based high-intensity aerobic interval-training program in patients with chronic heart failure. Am J Cardiol. 2008;102(9):1220-4.

40. Witham MD, Gray JM, Argo IS, Johnston DW, Struthers AD, McMurdo ME. Effect of a seated exercise program to improve physical function and health status in frail patients > or = 70 years of age with heart failure. Am J Cardiol. 2005;95(9):1120-4.

41. Witham MD, Fulton RL, Greig CA, et al. Efficacy and cost of an exercise program for functionally impaired older patients with heart failure: a randomized controlled trial. Circ Heart Fail. 2012;5(2):209-16.

42. Yeh GY, McCarthy EP, Wayne PM, et al. Tai Chi Exercise in Patients With Chronic Heart Failure: A Randomized Clinical Trial. Arch Intern Med. 2011;171(8):750-7.

43. Passino C, Severino S, Poletti R, et al. Aerobic Training Decreases B-Type Natriuretic Peptide Expression and Adrenergic Activation in Patients With Heart Failure. J Am Coll Cardiol. 2006;47(9):1835-9.

44. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation. 1999;99(9):1173-82.

45. McKelvie RS, Teo KK, Roberts R, et al. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT) Am Heart J. 2002;144(1):23-30.46. Willenheimer R, Rydberg E, Cline C, et al. Effects on quality of life, symptoms and daily activity 6 months after termination of an exercise training programme in heart failure patients. Int J Cardiol. 2001;77(1):25-31.

47. American Thoracic Society. Minnesota Living with Heart Failure Questionnaire 2004 [Available from: http://qol.thoracic.org/sections/instruments/ko/pages/mlwhfq.html.

48. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. J Eval Clin Pract. 2017;23(2):377-81.

49. Ciani O, Piepoli M, Smart N, Uddin J, Walker S, Warren FC, et al. Validation of Exercise Capacity as a Surrogate Endpoint in Exercise-Based Rehabilitation for Heart Failure: A Meta-Analysis of Randomized Controlled Trials. JACC Heart Fail. 2018;6(7):596-604.50. Flynn KE, Piña IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: Hf-action randomized controlled trial. JAMA. 2009;301(14):1451-9.

51. Mentz RJ, Bittner V, Schulte PJ, et al. Race, exercise training, and outcomes in chronic heart failure: findings from Heart Failure - a Controlled Trial Investigating Outcomes in Exercise TraiNing (HF-ACTION). Am Heart J. 2013;166(3):488-95.

52. Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet. 1993;341(8842):418-22.

53. Polanin JR. Efforts to retrieve individual participant data sets for use in a meta-analysis result in moderate data sharing but many data sets remain missing. J Clin Epidemiol. 2018;98:157-9.

54. Cowie MR, Wood DA, Coats AJ, et al. Incidence and aetiology of heart failure; a population-based study. Eur Heart J. 1999;20(6):421-8.

55. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13(1):132.

References

1. Braunwald E. The war against heart failure: the Lancet lecture. The Lancet. 2015;385(9970):812-24.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137-46.
3. BACPR. Standards and core components for cardiovascular disease prevention and rehabilitation 2017. Available from: www.bacpr.com/resources/6A7_BACR_Standards_and_Core_Components_2017.pdf.
4. Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. BMJ : British Medical Journal. 2015;351.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013;128(16):1810-52.
6. Kondamudi N, Haykowsky M, Forman DE, Berry JD, Pandey A. Exercise Training for Prevention and Treatment of Heart Failure. Progress in cardiovascular diseases. 2017;60(1):115-20.
7. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting Physical Activity and Exercise: JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(14):1622-39.
8. Taylor RS SV, Davies EJ, Briscoe S, Coats AJS, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. Cochrane Database of Systematic Reviews. 2014(4).
9. Uddin J, Zwisler AD, Lewinter C, Moniruzzaman M, Lund K, Tang LH, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis. Eur J Prev Cardiol. 2016;23(7):683-93.
10. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. The American journal of medicine. 2004;116(10):693-706.
11. Thompson S, Higgins J. How should meta-regression analyses be undertaken and interpreted? Statistics in Medicine. 2002;21(11):1559-73.
12. Chalmers I. The Cochrane Collaboration: Preparing, Maintaining, and Disseminating Systematic Reviews of the Effects of Health Care. Annals of the New York Academy of Sciences. 1993;703(1):156-65.
13. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ. 2004;328(7433):189.
14. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for a systematic review and meta-analysis of individual participant data: The prisma-ipd statement. JAMA. 2015;313(16):1657-65.
15. Tierney J, Vale C, Riley R, Tudur Smith C, Stewart L, Clarke M, et al. Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. PLoS Medicine. 2015;12(7):e1001855.
16. Taylor R, Piepoli M, Smart N, Coats A, Ellis S, Dalal H, et al. Exercise training for chronic heart failure (ExTraMATCH II): protocol for an individual participant data meta-analysis PROSPERO [Internet]. 2014. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42014007170.
17. Taylor RS, Piepoli MF, Smart N, Coats AJS, Ellis S, Dalal H, et al. Exercise training for chronic heart failure (ExTraMATCH II): Protocol for an individual participant data meta-analysis. International journal of cardiology. 2014;174(3):683-7.
18. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. European journal of heart failure. 2018.

19. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ. 2010;340.
20. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. BMJ. 2012;344.
21. Bilbao A, Escobar A, García-Perez L, Navarro G, Quirós R. The Minnesota living with heart failure questionnaire: comparison of different factor structures. Health and Quality of Life Outcomes. 2016;14:23.
22. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. Journal of the American College of Cardiology. 2000;35(5):1245-55.
23. Guyatt GH, Nogradi S, Halcrow S, Singer J, Sullivan MJJ, Fallen EL. Development and testing of a new measure of health status for clinical trials in heart failure. Journal of General Internal Medicine. 1989;4(2):101-7.
24. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure: HF-ACTION Randomized Controlled Trial. JAMA : the journal of the American Medical Association. 2009;301(14):1439-50.
25. Smart NA WM, Ismail H, Giallauria F, Vigorito C, Cornelissen V, Dieberg G. Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. International Journal of Evidence-Based Healthcare. 2015;13(1):9-18.
26. Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine. 2002;21(11):1539-58.
27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
28. Davidson PM, Cockburn J, Newton PJ, Webster JK, Betihavas V, Howes L, et al. Can a heart failure-specific cardiac rehabilitation program decrease hospitalizations and improve outcomes in high-risk patients? European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2010;17(4):393-402.
29. Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. European journal of heart failure. 2005;7(3):411-7.
30. Klecha A, Kawecka-Jaszcz K, Bacior B, Kubinyi A, Pasowicz M, Klimeczek P, et al. Physical training in patients with chronic heart failure of ischemic origin: effect on exercise capacity and left ventricular remodeling. European Journal of Cardiovascular Prevention & Rehabilitation. 2007;14(1):85-91.
31. Myers J, Goebbels U, Dzeikan G, Froelicher V, Bremerich J, Mueller P, et al. Exercise training and myocardial remodeling in patients with reduced ventricular function: One-year follow-up with magnetic resonance imaging. American heart journal. 2000;139(2, Part 1):252-61.
32. Mueller L, Myers J, Kottman W, Oswald U, Boesch C, Arbrol N, et al. Exercise capacity, physical activity patterns and outcomes six years after cardiac rehabilitation in patients with heart failure. Clinical rehabilitation. 2007;21(10):923-31.
33. Belardinelli R, Georgiou D, Cianci G, Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. J Am Coll Cardiol. 2012;60(16):1521-8.
34. Dracup K, Evangelista LS, Hamilton MA, Erickson V, Hage A, Moriguchi J, et al. Effects of a home-based exercise program on clinical outcomes in heart failure. American heart journal. 2007;154(5):877-83.
35. Gary RA, Dunbar SB, Higgins MK, Musselman DL, Smith AL. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. Journal of psychosomatic research. 2010;69(2):119-31.

36. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. Circulation. 2003;108(5):554-9.
37. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. Jama. 2000;283(23):3095-101.
38. Jolly K, Taylor RS, Lip GY, Davies M, Davis R, Mant J, et al. A randomized trial of the addition of home based exercise to specialist heart failure nurse care: the Birmingham Rehabilitation Uptake Maximisation study for patients with Congestive Heart Failure (BRUM-CHF) study. European journal of heart failure. 2009;11(2):205-13.
39. Nilsson BB, Westheim A, Risberg MA. Long-term effects of a group-based high-intensity aerobic interval training program in patients with chronic heart failure. The American journal of cardiology. 2008;102(9):1220-4.
40. Witham MD, Gray JM, Argo IS, Johnston DW, Struthers AD, McMurdo ME. Effect of a seated exercise program to improve physical function and health status in frail patients > or = 70 years of age with heart failure. The American journal of cardiology. 2005;95(9):1120-4.
41. Witham MD, Fulton RL, Greig CA, Johnston DW, Lang CC, van der Pol M, et al. Efficacy and cost of an exercise program for functionally impaired older patients with heart failure: a randomized controlled trial. Circulation Heart failure. 2012;5(2):209-16.
42. Yeh GY, McCarthy EP, Wayne PM, Stevenson LW, Wood MJ, Forman D, et al. Tai Chi Exercise in Patients With Chronic Heart Failure: A Randomized Clinical Trial. Archives of Internal Medicine. 2011;171(8):750-7.
43. Passino C, Severino S, Poletti R, Piepoli MF, Mammini C, Clerico A, et al. Aerobic Training Decreases B-Type Natriuretic Peptide Expression and Adrenergic Activation in Patients With Heart Failure. Journal of the American College of Cardiology. 2006;47(9):1835-9.
44. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation. 1999;99(9):1173-82.
45. McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, et al. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). American heart journal. 2002;144(1):23-30.
46. Willenheimer R, Rydberg E, Cline C, Broms K, Hillberger B, Oberg L, et al. Effects on quality of life, symptoms and daily activity 6 months after termination of an exercise training programme in heart failure patients. International journal of cardiology. 2001;77(1):25-31.
47. American Thoracic Society. Minnesota Living with Heart Failure Questionnaire 2004 [Available from: http://qol.thoracic.org/sections/instruments/ko/pages/mlwhfq.html.
48. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. Journal of Evaluation in Clinical Practice. 2017;23(2):377-81.
49. Ciani O, Piepoli M, Smart N, Uddin J, Walker S, Warren F, et al. Validation of exercise capacity as a surrogate endpoint in exercise-based rehabilitation for chronic heart failure: a meta-analysis of randomised controlled trials. JACC HF. in press.
50. Flynn KE, Piña IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: Hf-action randomized controlled trial. JAMA. 2009;301(14):1451-9.
51. Mentz RJ, Bittner V, Schulte PJ, Fleg JL, Pina IL, Keteyian SJ, et al. Race, exercise training, and outcomes in chronic heart failure: findings from Heart Failure - a Controlled Trial Investigating Outcomes in Exercise TraiNing (HF-ACTION). American heart journal. 2013;166(3):488-95.
52. Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? The Lancet. 1993;341(8842):418-22.

53. Polanin JR. Efforts to retrieve individual participant data sets for use in a meta-analysis result in moderate data sharing but many data sets remain missing. Journal of Clinical Epidemiology. 2018;98:157-9.
54. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, et al. Incidence and aetiology of heart failure; a population-based study. European heart journal. 1999;20(6):421-8.
55. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13(1):132.

Figure legends

Figure 1: PRISMA-IPD flow diagram

A PRISMA-IPD (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data) flow diagram to show selection and synthesis of ExTraMATCH II study data.

CENTRAL ILLUSTRATION: (Please see separate document for how we would like Figure 2 presented as the Central Illustration)

Figure 2. Effect of ExCR on HRQoL and exercise capacity at 12 months: two-stage IPD meta-analysis

A Forest plot from the two-stage IPD meta-analysis model to show the effect of ExCR on HRQoL and exercise capacity at 12 months

The black circle is centred on the point estimate of the effect of ExCR in each trial, with the horizontal line showing the 95% confidence interval (CI) of this estimate. An arrow to either the left or right shows that the CI extends beyond the area shown in the Forest Plot. The size of the grey square around the point estimate is proportional to the weight that the individual trial contributes to the meta-analysis. The diamond and vertical red line show the overall estimate of the effect of ExCR in the two-stage meta-analysis.

2a: Minnesota Living with Heart Failure Questionnaire (MLHFQ)

2b. All HRQoL measures (standardised score)

2c. Peak VO2, directly reported

2d. 6MWT, directly reported

2e. All exercise capacity measures (standardised score)

Figure 32. Effect of ExCR on HRQoL and exercise capacity at 6 months: two-stage IPD meta-analysis

The black circle is centred on the point estimate of the effect of ExCR in each trial, with the horizontal line showing the 95% confidence interval (CI) of this estimate. An arrow to either the left or right shows that the CI extends beyond the area shown in the Forest Plot. The size of the grey square around the point estimate is proportional to the weight that the individual trial contributes to the meta-analysis. The diamond and vertical red line show the overall estimate of the effect of ExCR in the two-stage meta-analysis.

32a: Minnesota Living with Heart Failure Questionnaire (MLHFQ)

32b. All HRQoL measures (standardised score)

32c. Peak VO2, directly reported

32d. 6MWT, directly reported

32e. All exercise capacity measures (standardised score)

~~Figure 3. Effect of ExCR on HRQoL and exercise capacity at 12 months: two-stage IPD meta-analysis~~

~~3a: Minnesota Living with Heart Failure Questionnaire (MLHFQ)~~

~~3b. All HRQoL measures (standardised score)~~

~~3c. Peak VO2, directly reported~~

~~3d. 6MWT, directly reported~~

~~3e. All exercise capacity measures (standardised score)~~

~~Online Figure 1. Effect of ExCR on HRQoL and exercise capacity~~

~~Online Figure 1a: Minnesota Living with Heart Failure Questionnaire (MLHFQ)~~

~~Online Figure 1b. All HRQoL measures (standardised score)~~

~~Online Figure 1c. Peak VO2, directly reported~~

~~Online Figure 1d. 6MWT, directly reported~~

~~Online Figure 1e. All exercise capacity measures (standardised score)~~

~~Online Figure 2: Funnel plots (12 months)~~

~~Online Figure 2a: Minnesota Living with Heart Failure Questionnaire (MLHFQ)~~

~~Footnote: Egger test -1.40, p=0.656~~

~~Online Figure 2b. All HRQoL measures (standardised score)~~

~~Footnote: Egger test -0.72, p=0.577~~

~~Online Figure 2c. Peak VO2, directly reported~~

~~Footnote: Egger test 0.99, p=0.665~~

~~Online Figure 2d. 6MWT, directly reported~~

~~Footnote: Egger test 1.71, p=0.150~~

~~Online Figure 2e. All exercise capacity measures (standardised score)~~

~~Footnote: Egger test 1.85, p=0.214~~

~~Online Figure 3: Effect of ExCR on HRQoL across patient subgroups (12 months)~~

~~Online Figure 3a: Minnesota Living with Heart Failure Questionnaire (MLHFQ)~~

~~Online Figure 3b. All HRQoL measures (standardised score)~~

~~Online Figure 4: Effect of ExCR on exercise capacity across patient subgroups~~

~~Online Figure 4a. Peak VO2, directly reported~~

~~Online Figure 4b. 6MWT, directly reported~~

~~Online Figure 4c. All exercise capacity measures (standardised score)~~

Tables

Table 1: Baseline characteristics of patients

Characteristic	**ExCR (n=1,662)**	**Control (n=1,670)**	**All (n=3,332)**
Age (years); mean (SD)	60.9 (13.2)	61.2 (13.5)	61.1 (13.4)
Gender			
Male	1,187 (71.4)	1,237 (74.1)	2,424 (72.8)
Female	475 (28.6)	433 (25.9)	908 (27.3)
Baseline ejection fraction (%); mean (SD)	27.0 (8.8)	26.9 (8.7)	26.9 (8.8)
Baseline ejection fraction:			
HFrEF (< 45%)	1,721 (96.8)	1,744 (97.5)	3,465 (97.1)
HFpEF (≥ 45%)	57 (3.2)	45 (2.5)	102 (2.9)
NYHA status			
Class I	20 (1.2)	25 (1.5)	45 (1.4)
Class II	1,002 (61.2)	1,032 (62.8)	2,034 (62.0)

Class III	597 (36.5)	569 (34.6)	1,166 (35.5)
Class IV	19 (1.2)	18 (1.1)	37 (1.1)
Aetiology			
Ischaemic	892 (54.9)	884 (54.1)	1,776 (54.5)
Non-ischemic	732 (45.1)	750 (45.9)	1,482 (45.5)
Ethnicity			
White	1,085 (69.3)	1,117 (70.9)	2,202 (70.1)
Non-white	480 (30.7)	458 (29.1)	938 (30.0)
MLHFQ; mean (SD)	35.6 (23.7)	33.6 (25.6)	34.6 (24.7)
Peak VO_2 (ml/kg/min); mean (SD)	15.0 (4.5)	15.1 (4.7)	15.0 (4.6)
6MWT (metres); mean (SD)	362.6 (109.3)	362.5 (112.1)	362.6 (110.7)

HFrEF: Heart Failure with reduced Ejection Fraction; HFpEF: Heart Failure with preserved Ejection Fraction; NYHA: New York Heart Association classification; MLHFQ: Minnesota Living with Heart Failure Questionnaire; peak VO_2: peak oxygen uptake; 6MWT: 6-minute walk test.

Table 2. Characteristics of included studies and interventions

Study characteristics	**n (%) of 14 comparators**
Publication year	
1990 to 1999	0 (0)
2000 to 2009	9 (64)
2010 to 2012	5 (36)
Unpublished	0 (0)
Main study location	
Europe	9 (64)
North America*	5 (36)
Single study centre	
Single	10 (71)
Multiple	4 (29)
Sample size	
0 to 99	8 (57)
100 to 999	5 (36)
1000 and over	1 (7)
Duration of latest follow up (weeks); median (range)	
HRQoL outcomes	33 (26 to 104)
Exercise capacity outcomes	26 (9 to 520)
Intervention characteristics	
Intervention type	
Exercise only programs	9 (64)
Comprehensive programs	5 (36)

Type of exercise	
Aerobic exercise only	10 (71)
Aerobic plus resistance training	4 (29)
Dose of intervention	
Duration of intervention (weeks), median (range)	24 (4 to 120)
Frequency (sessions per week), median (range)	3 (2 to 7)
Length of exercise session (mins), median (range)	30 (15 to 60)
Exercise intensity, range	40-70% peak VO_2 11-15 Borg rating
Setting	
Centre-based only	9 (64)
Home-based only	5 (36)

Online Table 1. Assessment of quality using TESTEX scale of included studies in IPD meta-analysis

Study (publication year)	Eligibility Criteria Specified	Randomisation Specified	Allocation Concealed	Groups Similar at baseline	Blinding of Assessors	Outcome measures in >85% participants	Intention to treat (ITT) analysis (2)	Between group statistical	Point measures & measures of	Activity monitoring in control group	Relative Exercise intensity reviewed	Exercise Volume and Energy Expended	Overall TESTEX score (maximum
Belardinelli (2012)	1	0	0	1	0	3	1	1	1	0	0	1	9
Dracup (2007)	1	0	0	1	0	3	1	2	1	1	1	1	10
Gary (2010)	1	1	0	1	1	3	1	2	1	0	0	0	11
Giannuzzi (2003)	1	0	0	1	0	2	1	2	1	0	1	1	10
Hambrecht (2000)	1	1	0	1	0	3	0	2	1	0	1	1	11

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

HF-Action (2008)	1	1	1	1	1	3	1	2	1	1	0	1	14
Jolly (2009)	1	1	1	1	0	2	1	2	1	0	1	1	12
Mueller (2007)	1	0	0	1	0	2	1	2	1	0	1	1	10
Nilsson (2008)	1	1	0	1	1	2	1	2	1	0	0	1	11
Passino (2006)	1	0	0	1	0	2	1	2	1	0	1	1	10
Witham (2005)	1	1	0	1	1	3	1	2	1	0	1	0	12
Witham (2012)	1	1	0	1	1	3	1	2	1	0	1	0	12

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~Yeh (2011)~~	~~1~~	~~1~~	~~0~~	~~1~~	~~1~~	~~3~~	~~1~~	~~2~~	~~1~~	~~1~~	~~0~~	~~0~~	~~12~~

~~(1) Three points possible; (2) If ITT was not specifically mentioned, but it was noted that no participants withdrew and all analysed, the analysis was considered to be ITT.~~

Formatted: Space After: 10 pt

Formatted: Normal, No bullets or numbering

Online Table 2. Minnesota Living with Heart Failure Questionnaire (MLHFQ) - overall treatment effect and subgroups effects

	Primary analyses				Sensitivity analyses, excluding HF-Action			
-	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value

Formatted: Space After: 10 pt

Formatted: Left, Space After: 10 pt

Formatted: Space After: 10 pt

Overall effect	-2.85 (-5.85, 0.14), p=0.062	-1.73 (-4.15, 0.70), p=0.163	-5.94 (-10.87, -1.01), p=0.018	-5.73 (-12.38, 0.93), p=0.091	Not applicable to MLHF analyses as HF-Action only supplied KCCQ scores			
Age (years)	0.12 (-0.10, 0.35), p=0.280		0.01 (-0.20, 0.22), p=0.912					
Gender (male vs female)	-5.31 (-11.01, 0.39), p=0.068		-1.49 (-6.95, 3.96), p=0.592					
Ejection fraction (%)	0.22 (-0.14, 0.58), p=0.227		0.24 (-0.07, 0.56), p=0.127					
Ejection Fraction	4.06 (-11.0, 19.1),		8.02 (-3.29, 19.3), p=0.165					

Formatted: Space After: 10 pt

Formatted: Left, Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~(HFpEF vs HFrEF)~~	~~p=0.597~~							
~~NYHA class (NYHA III/IV vs NYHA I/II)~~	~~-6.38 (-12.31, -0.45), p=0.035~~		~~-5.30 (-10.9, 0.24), p=0.061~~					
~~HF aetiology (ischaemic vs non-ischaemic)~~	~~4.67 (-1.65, 11.0), p=0.147~~		~~2.08 (-3.64, 7.80), p=0.477~~					
~~Ethnic group (white vs non-white)~~	~~3.15 (-4.31, 10.6), p=0.408~~		~~5.17 (-2.19, 12.5), p=0.169~~					
~~**Exercise capacity**~~								
~~Peak VO_2~~	~~0.24 (-0.82,~~		~~0.47 (-0.35,~~					

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~directly measured~~	~~1.31), p=0.654~~		~~1.29), p=0.262~~					
~~Peak VO_2, directly measured and predicted~~	~~0.72 (-0.01, 1.45), p=0.053~~		~~0.62 (-0.02, 1.26), p=0.058~~					

~~HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; NYHA: New York Heart Association classification; peak VO_2: peak oxygen uptake.~~

Formatted: Space After: 10 pt

Online Table 3. Standardised Health-related Quality of Life (HRQoL) measure- overall treatment effect and subgroups effects

	Primary analyses				Sensitivity analyses, excluding HF-Action			
-	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value

Formatted: Space After: 10 pt

Formatted: Left, Space After: 10 pt

Formatted: Space After: 10 pt

Overall effect	-0.11 (-0.16, -0.06), p<0.001	-0.10 (-0.15, -0.05), p<0.001	-0.20 (-0.37, -0.03), p=0.020	-0.19 (-0.38, -0.01), p=0.043	-0.11 (-0.24, 0.01), p=0.069	-0.08 (-0.18, 0.02), p=0.131	-0.17 (-0.28, -0.07), p=0.001 (*)	-0.21 (-0.45, 0.04), p=0.106
Age (years)	0.006 (0.002, 0.011), p=0.006		0.001 (-0.004, 0.005), p=0.734		0.003 (-0.007, 0.014), p=0.536		-0.001 (-0.011, 0.008), p=0.788	
Gender (male vs female)	0.050 (-0.068, 0.168), p=0.407		0.018 (-0.105, 0.140), p=0.775		-0.223 (-0.469, 0.024), p=0.077		-0.106 (-0.335, 0.123, p=0.365	
Ejection fraction (%)	-0.000 (-0.007, 0.007),		-0.004 (-0.011, 0.004), p=0.340		0.010 (-0.006, 0.025), p=0.225		0.010 (-0.003, 0.023),	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

	p=0.963						p=0.150	
Ejection Fraction (HFpEF vs HFrEF)	-0.03 (-0.46, 0.41), p=0.902		0.13 (-0.26, 0.53), p=0.505		0.16 (-0.47, 0.84), p=0.581		0.34 (-0.14, 0.81), p=0.163	
NYHA class (NYHA III/IV vs NYHA I/II)	-0.013 (-0.126, 0.100), p=0.824		0.031 (-0.086, 0.149), p=0.599		-0.126 (-0.380, 0.129), p=0.334		-0.082 (-0.314, 0.151), p=0.491	
HF aetiology (ischaemic vs non-ischaemic)	0.076 (-0.036, 0.187), p=0.182		0.030 (-0.085, 0.145), p=0.611		0.220 (-0.055, 0.494), p=0.117		0.080 (-0.162, 0.322), p=0.517	
Ethnic group	0.041 (-		0.017 (-0.108,		0.173 (-0.172,		0.243 (-	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~(white vs non-white)~~	~~0.079, 0.161), p=0.506~~		~~0.142), p=0.787~~		~~0.519), p=0.325~~		~~0.086, 0.573), p=0.147~~	
~~**Exercise capacity**~~								
~~Peak VO_2 directly measured~~	~~-0.002 (-0.014, -0.011), p=0.775~~		~~0.008 (-0.005, 0.021), p=0.230~~		~~0.012 (-0.035, 0.059), 0.612~~		~~0.021 (-0.012, 0.055), p=0.216~~	
~~Peak VO_2, directly measured and predicted~~	~~0.000 (-0.012, 0.013), p=0.956~~		~~0.008 (-0.004, 0.021), p=0.208~~		~~0.023 (-0.010, 0.056), p=0.171~~		~~0.020 (-0.008, 0.048), p=0.172~~	
~~Standardised scores using~~	~~N/A as no further data available over analysis in row above~~							

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Left, Space After: 10 pt

~~peak VO_2,~~ ~~6MWT, ISWT~~ ~~units, and watts~~	

~~(*) Fixed effect on treatment with a random effect on study, due to non-convergence of the random treatment effect model.~~

~~HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; NYHA: New York Heart Association classification; peak VO_2: peak oxygen uptake; 6MWT: 6-minute walk test; ISWT: incremental shuttle walk test.~~

Online Table 4. Peak oxygen uptake (peak VO_2), directly measured - overall treatment effect and subgroups effects

	Primary analyses				Sensitivity analyses, excluding HF-Action			
-	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value

Formatted: Space After: 10 pt

Formatted: Left, Space After: 10 pt

Formatted: Space After: 10 pt

Overall effect	0.62 (-0.82, 2.07), p=0.397	0.69 (-0.24, 1.62), p=0.145	1.01 (-0.42, 2.44), p=0.168	1.14 (-0.05, 2.34), p=0.061	0.71 (-1.10, 2.52), p=0.444	0.77 (-0.73, 2.28), p=0.315	1.15 (-0.60, 2.90), p=0.196	1.26 (-0.31, 2.82), p=0.115
Age (years)	0.00 (-0.02, 0.02), p=0.980		-0.00 (-0.02, 0.14), p=0.646		-0.01 (-0.07, 0.04), p=0.628		-0.02 (-0.06, 0.03), p=0.415	
Gender (male vs female)	-0.25 (-0.78, 0.27), p=0.345		-0.57 (-1.11, -0.04), p=0.036		-0.67 (-2.47, 1.14), p=0.468		-0.42 (-1.80, 0.95), p=0.549	
Ejection fraction (%)	0.03 (0.00, 0.06), p=0.034		0.02 (-0.01, 0.05), p=0.157		0.05 (-0.04, 0.13), p=0.280		0.03 (-0.04, 0.11), p=0.349	
Ejection Fraction	0.07 (-1.88, 2.01),		-0.13 (-2.07, 1.81), p=0.897		-1.34 (-2.42, 5.09),		-0.19 (-3.34, 2.97),	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~(HFpEF vs HFrEF)~~	~~p=0.947~~				~~p=0.485~~		~~p=0.907~~	
~~NYHA class (NYHA III/IV vs NYHA I/II)~~	~~-0.10 (-0.58, 0.38), p=0.687~~		~~-0.25 (-0.75, 0.24), p=0.318~~		~~-0.50 (-2.13, 1.13), p=0.549~~		~~-0.75 (-1.95, 0.46), p=0.224~~	
~~HF aetiology (ischaemic vs non-ischaemic)~~	~~0.02 (-0.44, 0.47), p=0.945~~		~~-0.13 (-0.60, 0.34), p=0.577~~		~~-0.63 (-2.04, 0.79), p=0.386~~		~~-0.24 (-1.39, 0.91), p=0.683~~	
~~Ethnic group (white vs non-white)~~	~~-0.19 (-0.66, 0.29), p=0.447~~		~~-0.07 (-0.58, 0.45), p=0.800~~		~~-0.47 (-2.36, 1.43), p=0.628~~		~~0.16 (-1.71, 2.03), p=0.870~~	
~~**Exercise capacity**~~								
~~Peak VO_2~~	~~0.01 (-0.04,~~		~~0.03 (-0.03,~~		~~-0.06 (-0.21,~~		~~-0.04 (-0.17,~~	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~directly measured~~	~~0.06), p=0.719~~		~~0.08), p=0.332~~		~~0.09), p=0.435~~		~~0.10), p=0.602~~	
~~Peak VO_2, directly measured and predicted~~	~~0.01 (-0.04, 0.06), p=0.702~~		~~0.03 (-0.02, 0.08), p=0.299~~		~~-0.06 (-0.21, 0.09), p=0.452~~		~~-0.03 (-0.16, 0.10), p=0.660~~	

~~HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; NYHA: New York Heart Association classification; peak VO_2: peak oxygen uptake.~~

Formatted: Space After: 10 pt

Online Table 5. 6MWT directly measured - overall treatment effect and subgroups effects

	Primary analyses				Sensitivity analyses, excluding HF-Action			
-	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value

Formatted: Space After: 10 pt

Formatted: Left, Space After: 10 pt

Formatted: Space After: 10 pt

Overall effect	22.1 (1.87, 42.3), p=0.032	24.4 (6.13, 42.6), p=0.009	21.0 (1.57, 40.4), p=0.034	24.0 (5.30, 42.7), p=0.012	22.1 (-1.64, 45.8), p=0.068	27.9 (1.25, 54.6), p=0.040	24.0 (1.25, 46.7), p=0.039	29.0 (3.05, 55.0), p=0.029
Age (years)	0.01 (-0.49, 0.50), p=0.973		-0.03 (-0.56, 0.50), p=0.911		0.45 (-0.81, 1.72), p=0.482		0.97 (-0.23, 2.17), p=0.115	
Gender (male vs female)	-10.7 (-23.6, 2.26), p=0.106		-14.9 (-28.7, -1.16), p=0.034		-19.7 (-47.3, 7.92), p=0.162		-13.5 (-39.9, 12.9), p=0.317	
Ejection fraction (%)	0.34 (-0.46, 1.14), p=0.399		0.21 (-0.64, 1.06), p=0.634		1.05 (-0.78, 2.88), p=0.262		0.04 (-1.69, 1.77), p=0.963	
Ejection Fraction	0.68 (-47.8, 49.2),		15.4 (-36.3, 67.0), p=0.560		13.8 (-6.09, 88.6),		14.7 (-56.1, 85.4),	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

(HFpEF vs HFrEF)	p=0.978				p=0.717		p=0.685	
NYHA class (NYHA III/IV vs NYHA I/II)	-1.81 (-14.3, 10.6), p=0.776		1.31 (-12.0, 14.6), p=0.847		-5.90 (-34.6, 22.8), p=0.687		-8.14 (-35.7, 19.4), p=0.563	
HF aetiology (ischaemic vs non-ischaemic)	3.73 (-8.26, 15.7), p=0.542		-4.30 (-17.1, 8.51), p=0.510		37.9 (9.34, 66.4), p=0.009		26.9 (-0.13, 54.0), p=0.051	
Ethnic group (white vs non-white)	10.46 (-2.55, 23.5), p=0.115		14.2 (0.40, 28.0), p=0.044		-20.7 (-60.5, 19.0), p=0.307		8.34 (-29.5, 46.1), p=0.665	
Exercise capacity								
6MWT directly	-0.05 (-0.11,		0.19 (-0.08,		-0.06 (-0.18,		-0.05 (-0.16,	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

measured	0.01), p=0.079		0.46), p=0.176		0.06), p=0.321		0.07), p=0.421	

HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; NYHA: New York Heart Association classification; 6MWT: 6-minute walk test.

Online Table 6. Standardised exercise capacity score - overall treatment effect and subgroups effects

	Primary analyses				Sensitivity analyses, excluding HF-Action			
-	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 12 months FU Mean difference (95% CI) p-value	One-stage model, 6 months FU, with random treatment effect Mean difference (95% CI) p-value	Two-stage model, 6 months FU Mean difference (95% CI) p-value	One-stage model, 12 months FU, with random treatment effect Mean difference (95% CI)	Two-stage model, 12 months FU Mean difference (95% CI) p-value

Formatted: Space After: 10 pt

Formatted: Left, Space After: 10 pt

Formatted: Space After: 10 pt

							p-value	
Overall effect	0.230 (0.067, 0.392), p=0.006	0.256 (0.116, 0.396), p<0.001	0.268 (0.110, 0.426), p=0.001	0.302 (0.142, 0.462), p<0.001	0.256 (0.079, 0.433), p=0.005	0.278 (0.105, 0.451), p=0.002	0.298 (0.125, 0.471), p=0.001	0.324 (0.150, 0.497), p<0.001
Age (years)	0.001 (-0.003, 0.004), p=0.758		-0.001 (-0.005, 0.003), p=0.636		0.003 (-0.008, 0.014), p=0.565		-0.000 (-0.010, 0.009), p=0.948	
Gender (male vs	-0.063 (-0.157, 0.319),		-0.096 (-0.197, 0.006), p=0.065		-0.066 (-0.250, 0.118), p=0.484		-0.065 (-0.240, 0.110),	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~female)~~	~~p=0.194~~						~~p=0.464~~	
~~Ejection fraction (%)~~	~~0.007 (0.001, 0.012), p=0.021~~		~~0.005 (-0.001, 0.011), p=0.108~~		~~0.008 (-0.003, 0.019), p=0.131~~		~~0.008 (-0.003, 0.018), p=0.169~~	
~~Ejection Fraction (HFpEF vs HFrEF)~~	~~0.11 (-0.20, 0.43), p=0.487~~		~~0.06 (-0.28, 0.40), p=0.733~~		~~0.21 (-0.23, 0.65), p=0.348~~		~~0.06 (-0.36, 0.49), p=0.766~~	
~~NYHA class (NYHA III/IV vs NYHA I/II)~~	~~-0.010 (-0.098, 0.079), p=0.826~~		~~-0.043 (-0.138, 0.052), p=0.377~~		~~-0.011 (-0.184, 0.162), p=0.900~~		~~-0.061 (-0.224, 0.101), p=0.459~~	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~HF aetiology (ischaemic vs non-ischaemic)~~	~~0.012 (-0.074, 0.098), p=0.783~~		~~0.024 (-0.070, 0.117), p=0.620~~		~~0.035 (-0.143, 0.213), p=0.701~~		~~0.049 (-0.121, 0.219), p=0.573~~	
~~Ethnic group (white vs non-white)~~	~~-0.064 (-0.159, 0.031), p=0.187~~		~~0.018 (-0.088, 0.124), p=0.741~~		~~-0.096 (-0.352, 0.160), p=0.461~~		~~0.078 (-0.195, 0.351), p=0.577~~	
~~**Exercise capacity**~~								
~~Standardised scores using peak VO_2, 6MWT, ISWT units, and watts~~	~~-0.025 (-0.066, 0.017), p=0.240~~		~~-0.017 (-0.048, 0.508), p=0.105~~		~~-0.070 (-0.147, 0.007), p=0.077~~		~~-0.052 (-0.129, 0.026), p=0.191~~	

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

Formatted: Space After: 10 pt

~~Peak VO_2: peak oxygen uptake; ISWT: incremental shuttle walk test; 6MWT: 6-minute walk test~~